

Application No.: 10/622210

Docket No.: BP1-196

In the claims:

Please amend claims 1-3, 12-14, 16-17, 21, 28, and 29 as follows.

1. **(Currently amended)** A method of treating a subject suffering from vasculitis comprising administering a therapeutically effective amount of a human TNF $\alpha$  antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNF $\alpha$  with a  $K_d$  of  $1 \times 10^{-8}$  M or less and a  $K_{off}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, both determined by surface plasmon resonance, and neutralizes human TNF $\alpha$  cytotoxicity in a standard *in vitro* L929 assay with an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less, such that the vasculitis is treated.
2. **(Currently amended)** A method of treating a subject suffering from vasculitis comprising administering a therapeutically effective amount of a human TNF $\alpha$  antibody, or an antigen-binding fragment thereof, with the following characteristics:
  - a) dissociates from human TNF $\alpha$  with a  $K_{off}$  rate constant of  $1 \times 10^{-3} \text{ s}^{-1}$  or less, as determined by surface plasmon resonance;
  - b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;
  - c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, such that the vasculitis is treated.
3. **(Currently amended)** A method of treating a subject suffering from vasculitis comprising administering a therapeutically effective amount of a human TNF $\alpha$  antibody, or an antigen-binding fragment thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, such that the vasculitis is treated.

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4. **(Original)** The method of any one of claims 1, 2, and 3, wherein the antibody, or antigen-binding fragment thereof, is D2E7.
5. **(Original)** The method of any one of claims 1, 2, and 3, wherein the vasculitis is a large vessel disease.
6. **(Original)** The method of claim 5, wherein the large vessel disease is giant cell arteritis..
7. **(Original)** The method of any one of claims 1, 2, and 3, wherein the vasculitis is a medium vessel disease.
8. **(Original)** The method of claim 7, wherein the medium vessel disease is Kawasaki's Disease.
9. **(Original)** The method of any one of claims 1, 2, and 3, wherein the vasculitis is a small vessel disease.
10. **(Original)** The method of claim 8, wherein the small vessel disease is Behcet's syndrome or Wegener's granulomatosis.
11. **(Original)** The method of any one of claims 1, 2, and 3, wherein the vasculitis is selected from the group consisting of giant cell arteritis, temporal arteritis, polymyalgia rheumatica, Takayasu's disease, polyarteritis nodosa, Kawasaki's disease, Behcet's Syndrome, Wegener's granulomatosis, and Churg-Strauss syndrome.
12. **(Currently amended)** A method of treating vasculitis in a subject, wherein the vasculitis is selected from the group consisting of Behcet's disease, Wegener's granulomatosis, and giant cell arteritis, comprising administering a therapeutically effective amount of a human ~~TNF $\alpha$~~  antibody, or an antigen-binding fragment thereof, to the subject, wherein the antibody dissociates from human TNF $\alpha$  with a  $K_d$  of  $1 \times 10^{-8}$  M or less and a  $K_{off}$  rate constant of  $1 \times 10^{-3}$  s $^{-1}$  or less, both determined by surface plasmon resonance, and neutralizes human TNF $\alpha$ .

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cytotoxicity in a standard *in vitro* L929 assay with an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less, such that said vasculitis is treated.

13. **(Currently amended)** A method of treating vasculitis in a subject, wherein the vasculitis is selected from the group consisting of Behcet's disease, Wegener's granulomatosis, and giant cell arteritis, comprising administering a therapeutically effective amount of a human ~~TNF $\alpha$~~  antibody, or an antigen-binding fragment thereof, with the following characteristics:

a) dissociates from human TNF $\alpha$  with a  $K_{off}$  rate constant of  $1 \times 10^{-3} s^{-1}$  or less, as determined by surface plasmon resonance;

b) has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3, or modified from SEQ ID NO: 3 by a single alanine substitution at position 1, 4, 5, 7 or 8 or by one to five conservative amino acid substitutions at positions 1, 3, 4, 6, 7, 8 and/or 9;

c) has a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4, or modified from SEQ ID NO: 4 by a single alanine substitution at position 2, 3, 4, 5, 6, 8, 9, 10 or 11 or by one to five conservative amino acid substitutions at positions 2, 3, 4, 5, 6, 8, 9, 10, 11 and/or 12, such that said vasculitis is treated.

14. **(Currently amended)** A method of treating vasculitis in a subject, wherein the vasculitis is selected from the group consisting of Behcet's disease, Wegener's granulomatosis, and giant cell arteritis, comprising administering a therapeutically effective amount of a human ~~TNF $\alpha$~~  antibody, or an antigen-binding fragment thereof, with a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2, such that said vasculitis is treated.

15. **(Original)** The method of any one of claims 12, 13 or 14, wherein the antibody, or antigen-binding fragment thereof, is D2E7.

16. **(Currently amended)** A method for inhibiting human TNF $\alpha$  activity in a human subject suffering from vasculitis comprising administering a therapeutically effective amount of a human ~~TNF $\alpha$~~  antibody, or an antigen-binding fragment thereof, to the subject, wherein the

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antibody dissociates from human TNF $\alpha$  with a  $K_d$  of  $1 \times 10^{-8}$  M or less and a  $K_{off}$  rate constant of  $1 \times 10^{-3}$  s $^{-1}$  or less, both determined by surface plasmon resonance, and neutralizes human TNF $\alpha$  cytotoxicity in a standard *in vitro* L929 assay with an IC $_{50}$  of  $1 \times 10^{-7}$  M or less.

17. **(Currently amended)** The method of claim 16, wherein the ~~TNF $\alpha$~~  antibody, or antigen binding fragment thereof, is D2E7.
18. **(Original)** The method of claim 16 or 17, wherein the vasculitis is giant cell arteritis.
19. **(Original)** The method of claim 16 or 17, wherein the vasculitis is Kawasaki's Disease.
20. **(Original)** The method of claim 16 or 17, wherein the vasculitis is Behcet's Syndrome or Wegener's granulomatosis.
21. **(Currently amended)** A method for inhibiting human TNF $\alpha$  activity in a human subject suffering vasculitis selected from the group consisting of Behcet's disease, Wegener's granulomatosis, and giant cell arteritis, comprising administering a therapeutically effective amount of a human ~~TNF $\alpha$~~  antibody, or an antigen-binding fragment thereof, to the subject wherein the antibody dissociates from human TNF $\alpha$  with a  $K_d$  of  $1 \times 10^{-8}$  M or less and a  $K_{off}$  rate constant of  $1 \times 10^{-3}$  s $^{-1}$  or less, both determined by surface plasmon resonance, and neutralizes human TNF $\alpha$  cytotoxicity in a standard *in vitro* L929 assay with an IC $_{50}$  of  $1 \times 10^{-7}$  M or less.
22. **(Original)** The method of claim 21, wherein the antibody, or antigen binding fragment thereof, is D2E7.
23. **(Original)** A method of treating a subject suffering from vasculitis selected from the group consisting of large vessel disease, medium vessel disease, and small vessel disease,

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comprising administering a therapeutically effective amount of D2E7, or an antigen-binding fragment thereof, to the subject, such that vasculitis is treated.

24. (Original) The method of claim 23, wherein the large vessel disease is giant cell arteritis.

25. (Original) The method of claim 23, wherein the medium vessel disease is Kawasaki's Disease.

26. (Original) The method of claim 23, wherein the small vessel disease is Behcet's Syndrome or Wegener's granulomatosis.

27. (Original) A method of treating a subject suffering from vasculitis selected from the group consisting of Behcet's disease, Wegener's granulomatosis, and giant cell arteritis, comprising administering a therapeutically effective amount of D2E7, or an antigen-binding fragment thereof, to the subject, such that said vasculitis is treated.

28. (Currently amended) A kit comprising:  
a) a pharmaceutical composition comprising a human TNF $\alpha$  antibody, or an antigen binding portion thereof, and a pharmaceutically acceptable carrier, wherein the antibody dissociates from human TNF $\alpha$  with a  $K_d$  of  $1 \times 10^{-8}$  M or less and a  $K_{off}$  rate constant of  $1 \times 10^{-3}$  s $^{-1}$  or less, both determined by surface plasmon resonance, and neutralizes human TNF $\alpha$  cytotoxicity in a standard *in vitro* L929 assay with an  $IC_{50}$  of  $1 \times 10^{-7}$  M or less; and  
b) instructions for administering to a subject the TNF $\alpha$  antibody pharmaceutical composition for treating a subject who is suffering from vasculitis.

29. (Currently amended) A kit according to claim 28, wherein the TNF $\alpha$  antibody, or an antigen binding portion thereof, is D2E7.